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LETTER TO THE EDITORS

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Prepulse lost and regained: a commentary on "Weak prepulses inhibit but do not elicit startle in rats and humans" *Biological Psychiatry* 55:98–101

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Swerdlow et al. (2004) addressed in their recent paper the possible relation between prepulse-elicited reactivity and prepulse inhibition, which was raised by Dahmen and Corr (2004) in healthy human subjects and by us in mice (Yee et al. 2004a,b). In their report, Swerdlow and colleagues showed that prepulse inhibition (PPI) can be reliably demonstrated with prepulses that do not generate observable reactivity by employing (unusually) weak prepulses in the range of 1–5 dB above background noise. Whilst we concur that the presence of measurable prepulse-elicited reactivity is not a prerequisite for the generation of PPI, we feel that it is premature to discourage speculation concerning the potential theoretical and practical relevance of prepulse-elicited response measures to PPI. Because of this and our shared interest in the psychopharmacology of prepulse processing with respect to the expression of PPI, we feel obliged to add a few clarifications concerning the relevance of our data (Yee et al. 2004a) cited by Swerdlow and colleagues in their report.

First, although the positive correlation we obtained between prepulse-elicited reactivity (4–16 dB above background) and PPI magnitude in mice was opposite to the relationship reported by Dahmen and Corr (2004) between prepulse response probability and PPI in humans, our finding on the effects of apomorphine (2 mg/kg, s.c.) is in agreement with the relationship described by Dahmen and Corr (2004): apomorphine reduces PPI and concomitantly enhances prepulse-elicited reactivity (see Fig. 1, Yee et al. 2004a, pp. 243).

Second, contrary to their claim, it is our view that the effect of apomorphine (0.5 mg/kg, s.c.) reported by Swerdlow et al. (2004) is not consistent with what we demonstrated previously in mice (Yee et al. 2004a). Swerdlow and colleagues elected to emphasize the non-significant elevation of reactivity obtained on trials without any explicit stimulus (i.e., "no stimulus" trials) in our Experiments 1 and 3 (the percentage elevation for Experiment 3 should be 37.2%, but not 46.3% as mistakenly calculated by Swerdlow et al. on the basis of Table 1 in Yee et al. 2004a). What has been overlooked is that against this *non-significant* change in reactivity on no-stimulus trials, apomorphine led to a *significant* increase in the reactivity in prepulse-alone trials including the weakest prepulse at +4 dB over background (see Figs. 1c and 3c, Yee et al. 2004a). Hence, their conclusion that apomorphine "does not selectively affect these [prepulse-related] variables on trials with prepulses" (Swerdlow et al. 2004, p. 1196) does not apply to our data.

This is also the case when we re-examined our data (Experiment 1, Yee et al. 2004a) using the measure of "response probability" following the definition by Dahmen and Corr (2004), as did Swerdlow et al. (2004). Expressed as response probability deviation from no-stimulus trials, we obtained a clear effect [$F(1,77)=8.00$, $p=0.006$] of apomorphine across all prepulse intensities examined including the weakest +4 dB prepulse (see Fig. 1 here). Again, this contrasts with Swerdlow et al.'s observation that "in apomorphine-treated rats, prepulses alone did not increase either response probability or mean motor activity compared with no stimulus" (Swerdlow et al. 2004, p. 1197).

Third, with the specific aim to examine weak prepulses alone, Swerdlow et al. (2004) had excluded prepulses of higher magnitude. This is unfortunate because PPI studies in both human and animals typically employ prepulse extending up to +16 dB over background. In the literature, conclusions have been drawn based on effects on PPI that were only clearly seen at prepulse intensities that are clearly not weak by Swerdlow et al.'s standard. Thus, the possibility that prepulse-elicited reactivity may be a confounding (though may not be causally related, see Yee et al. 2004b) variable in human and rodent measures of PPI needs to be considered seriously.

Lastly, given that the apparatus routinely employed is not designed to measure the low-level response expected from prepulse-alone presentation, it is not surprising that at

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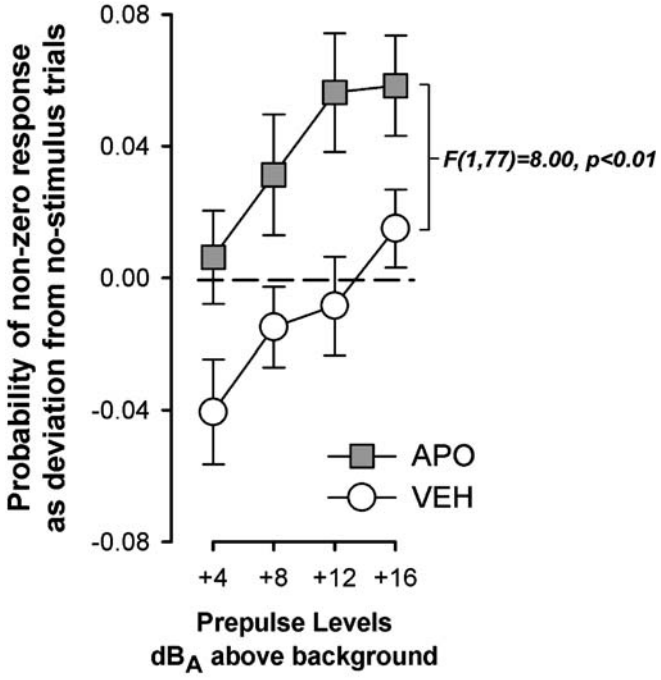

Fig. 1 The effect of systemic apomorphine (2 mg/kg, s.c.) on prepulse-elicited response as reported in Experiment 1 of Yee et al. (2004a) was expressed using the measure of "response probability", as described by Dahmen and Corr (2004). Here, prepulse-elicited reactivity on each of the four prepulse intensities is depicted as deviation from that obtained on no-stimulus trials. A 2×4 (drug treatment × prepulse levels) ANOVA yielded a clear main effect of drug treatment, which was consistent with the conclusion based on a more direct measure of response magnitude as described in the original report. *Error bars* refer to ±SEM

sufficiently low intensities prepulse alone may not yield clearly observable reaction beyond the baseline (no stimulus) level. The conceptual distinction between weak and non-weak prepulses therefore warrants critical examination. Technical advances in the future will allow a closer and more accurate characterization of prepulse-elicited reaction in the context of PPI, and we encourage additional experiments in this direction.

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